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Original Investigation

Association of gestational weight gain with maternal and infant adverse outcomes

LifeCycle Project - Maternal Obesity and Childhood Outcomes Study Group

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KEY POINTS

Question: What is the association of gestational weight gain, across a range of pre-pregnancy weights, with maternal and infant outcomes?

Findings: In this meta-analysis of individual participant data from 25 pooled cohort studies and 196670 participants, pre-pregnancy weight and the magnitude of gestational weight gain were associated with risk of adverse outcomes (defined as pre-eclampsia, gestational hypertension, gestational diabetes, caesarean section, preterm birth, and small or large size-for-gestational-age at birth), although the magnitude of weight gain was weakly associated with the adverse outcomes assessed.

Meaning: These findings may inform prenatal counseling regarding optimal weight gain during pregnancy, although the magnitude of weight gain was weakly associated with the outcomes assessed.

ABSTRACT

Importance: Both low and high gestational weight gain have been associated with adverse maternal and infant outcomes, but optimal gestational weight gain ranges remain uncertain and not well defined for all pre-pregnancy weights.

Objective: To examine the association of ranges of gestational weight gain with risks of adverse maternal and infant outcomes and to estimate optimal gestational weight gain ranges across a range of pre-pregnancy weights.

Design, Setting, and Participants: Individual participant data meta-analysis using data from 196670 participants from 25 cohort studies from Europe and North-America (main study-sample). Optimal gestational weight gain ranges were estimated for each pre-pregnancy BMI category by selecting the range of gestational weight gain that was associated with lower risk for the main endpoint, defined as 'any adverse outcome'. Individual participant data from 3505 participants from 4 separate hospital-based cohorts were used as validation sample. Data were collected between 1989 and 2015. Final date of follow-up was December 2015.

Exposures: Gestational weight gain.

Main Outcomes and Measures: 'Any adverse outcome', defined as the presence of one or more of the following outcomes: pre-eclampsia, gestational hypertension, gestational diabetes, caesarean section, preterm birth, small or large size-for-gestational-age at birth.

Results: Of the 196670 women included in the main sample, 7809 (4.0%), 133788 (68.0%), 38828 (19.7%), 11992 (6.1%), 3284 (1.7%) and 969 (0.5%) were underweight, normal weight, overweight, obesity grade 1, obesity grade 2 and obesity grade 3 at baseline, respectively. Overall, any adverse outcome occurred in 37.2% (n=73161) of women, ranging from 34.7% (n=2706) in women with underweight to 61.1% (n=592) in women with obesity grade 3. Optimal weight gain ranges were 14.0-<16.0 kg for underweight, 10.0-<18.0 kg for normal weight, 2.0-<16.0 kg for overweight, 2.0-<6.0 kg for obesity grade 1, weight loss- weight gain of <4.0 kg for obesity grade 2, and 0.0-<6.0 kg for obesity grade 3. These ranges were associated with low to moderate discrimination between those with and without adverse outcomes (Areas-under-the-curve (AUCs): 0.546-0.759). Results for discriminative performance in the validation sample were similar to corresponding results in the main study-sample (AUCs: 0.506-0.787).

Conclusions and Relevance: In this meta-analysis of pooled individual participant data from 25 cohort studies, the risk of adverse maternal and infant outcomes varied by gestational weight gain and across the range of pre-pregnancy weights. The estimates of optimal gestational weight gain may inform prenatal counseling, although the optimal weight gain ranges had limited predictive value for the outcomes assessed.

INTRODUCTION

Gestational weight gain has been related to the risks of pregnancy complications, maternal postpartum weight retention and offspring obesity.[1-3] Gestational weight gain reflects multiple characteristics, including maternal fat accumulation, fluid expansion, and growth of the fetus, placenta and uterus.[4] Gestational weight gain is necessary to ensure a healthy fetus, but excessive gestational weight gain has been associated with adverse outcomes. Higher pre-pregnancy body mass index (BMI) has also been associated with lower gestational weight gain, as well as with increased risks of adverse maternal and infant outcomes. Therefore, optimal gestational weight gain ranges need to account for pre-pregnancy BMI.[5,6] Existing guidelines for gestational weight gain by the US Institute of Medicine (IOM) have limitations including reliance on a limited number of observational studies relating gestational weight gain to five maternal and offspring outcomes and insufficient information about important pregnancy outcomes, including gestational hypertension and gestational diabetes.[7] In addition, these guidelines do not include recommendations for obesity grades 1 to 3 separately, even though the prevalence of extreme obesity is rising in Western populations. Information regarding optimal gestational weight gain across a range of maternal BMI categories is important for identification of groups at increased risk in obstetric care.

This study pooled individual participant data from 25 pregnancy and birth cohorts from Europe and North-America to assess the associations of the amount of weight gain with maternal and infant outcomes according to baseline weight status of underweight, normal weight, overweight, obesity grade 1, obesity grade 2 and obesity grade 3.

METHODS

Inclusion criteria and participating cohorts

This study was part of an international LifeCycle Project collaboration on Maternal Obesity and Childhood Outcomes (MOCO).[8,9] Pregnancy and birth cohort studies were eligible for inclusion if they included mothers with singleton live-born children born between 1989 and 2015, had information on maternal pre- or early-pregnancy BMI and had at least one offspring measurement (birth weight or childhood BMI). No exclusions were made based on previous pregnancy- or birth complications. Cohorts included were approved by their local institutional review boards and written informed consent was obtained from participants. We invited 50 Western cohorts from Europe, North America and Oceania, selected from existing collaborations on childhood health (EarlyNutrition Project, CHICOS Project, www.birthcohorts.net assessed until July 2014), of which 39 agreed to participate. Only participants with information on maternal pre-pregnancy BMI, gestational weight gain and at least one maternal or infant outcome of interest were included (n=200175 participants from 29 cohorts). Of the 29 cohorts with required data, 25 (n=196670) were population-based and were included as main study sample. The remaining 4 cohorts were hospital-based, and were included as external validation sample (n=3505, **eFigure 1**). **eTable 1** lists included cohorts with their data collection methods. Women could be included more than once in the analyses if they had multiple singleton pregnancies during the study period of a specific cohort. Anonymized datasets were stored on a single central secured data server with access for the main analysts (EV, RG).

Maternal pre-pregnancy BMI and gestational weight gain

Maternal pre-pregnancy BMI (kg/m^2) was grouped into categories of 2 kg/m^2 and into clinical BMI groups according to World Health Organization (WHO) definitions.[10] Data on total gestational weight gain (kg), defined as the difference between the latest weight before delivery and pre-pregnancy weight, was provided by cohorts. Gestational weight gain was grouped into categories of 2 kg each, ranging from weight loss to weight gain of ≥28 kg. Smaller increments of gestational weight gain were not used because of insufficient statistical power among underweight and severely obese women. Categories at the extremes of gestational weight gain were combined for maternal underweight, obesity grade 2, and obesity grade 3. All women had information on maternal pre-pregnancy BMI, total gestational weight gain and presence or absence of an adverse outcome (defined below).

Maternal and infant adverse outcomes

Adverse outcomes were pre-eclampsia, gestational hypertension, gestational diabetes, preterm birth, small size-for-gestational-age at birth, large size-for-gestational-age at birth, and caesarean section. Preterm birth was defined as gestational age at birth <37 weeks. Sex- and gestational age-adjusted standard-deviation (SD) scores for birth weight were calculated using a North-European reference chart.[11] Small and large size-for-gestational-age at birth were defined as sex- and gestational-age-adjusted birth weight $<10^{th}$ percentile and $>90^{th}$ percentile, respectively, within each cohort. The main outcome of analyses was the composite 'any adverse outcome', defined as the presence of at least one of the outcomes described above.

For sensitivity analyses, sex- and age-adjusted SD scores were calculated for childhood BMI based on WHO reference growth charts.[12,13] SD scores were obtained using data from the highest age available for each child (median age (Q1, Q3): 84.9 months (61.9, 95.9)) and categorized into underweight, normal weight, or overweight/obesity (referred to as overweight) using WHO cut-offs.[12,13]

Statistical analysis

First, we used exploratory multilevel linear regression models to assess associations of maternal baseline characteristics with total gestational weight gain. Second, we estimated the absolute risks of any adverse outcome across the full range of maternal pre-pregnancy BMI and gestational weight gain. Absolute risks were calculated as percentage of women with any adverse outcome within each combination of BMI and gestational weight gain categories. Similarly, we estimated the absolute risks of any adverse outcome and each individual outcome across the range of gestational weight gain categories, within each clinical BMI group. Third, we constructed ranges of optimal weight gain per clinical BMI group. We calculated the Odds Ratios (ORs) of any adverse outcome for each gestational weight gain category within a clinical BMI group, as compared to all other mothers within that BMI group. We analysed individual level data from all cohorts simultaneously using multilevel models. Our models followed a two-level hierarchical structure with participants (level 1) nested within cohorts (level 2). We used generalized linear mixed model with a binominal distribution and logit link. We included a random intercept at cohort level to allow variation in the baseline risk of each cohort. Allowing a random slope for gestational weight gain did not improve the models. Model assumptions regarding linearity, independent errors and influential values were met. We defined optimal gestational weight gain as all weight gain categories with a statistically significant protective association (OR below one) for any adverse outcome.[14] If a weight gain category with a non-significant association was between two significant estimates with an OR below one, that category was included in the optimal weight gain range. To construct easily interpretable optimal weight gain ranges applicable for clinical practice, these main analyses were not adjusted for maternal age or parity. We also assessed continuous associations of maternal pre-pregnancy BMI and total gestational weight gain in SDS with any adverse outcome and compared the strength of these associations by testing the difference in ORs. We performed six sensitivity analyses: 1) We re-defined the gestational weight gain ranges based on protective associations (OR below one) only, regardless of statistical significance; 2) As gestational weight gain depends on length of gestation, we adjusted the models for gestational age at birth and performed a sensitivity analysis excluding pre-term births; 3) A sensitivity analysis was performed excluding participants with missing data on separate adverse maternal and infant outcomes.; 4) To explore whether optimal ranges would change when maternal age and parity were taken into account, we performed a sensitivity analysis adjusting for maternal age and parity. 5) To explore whether optimal ranges would change depending on the definition of the composite outcome, we performed additional analyses excluding caesarean section as an adverse outcome and additional analyses including childhood underweight and overweight as adverse outcomes; 6) To address possible reverse causation, we performed analyses excluding pre-eclampsia and gestational diabetes as outcomes. We also constructed optimal gestational weight gain ranges for weight gain in the first half of pregnancy, defined as the difference between weight at median gestational age of 15.4 weeks (Q1, Q3: 13.2, 17.1) and pre-pregnancy weight, using a similar approach.

Next, as secondary analyses, we assessed the clinical performance of the ranges of this study, compared to the IOM classification, by assessing the number of participants classified as having inadequate or excessive weight gain, the associations with adverse outcomes using binary logistic multilevel models and the discriminative performance for both classifications. We assessed the discriminative performance of the classification from this study and the IOM, which is the ability of the classification to discriminate between those with and without the outcome, based on areas under the Receiver Operator Characteristic curve (AUC).[15] We obtained predicted probabilities from binary logistic multilevel models assessing the associations of inadequate and excessive gestational weight gain with the outcomes. These predicted probabilities were used to calculate Receiver Operator Characteristic (ROC) curves and AUC. To assess the associations of the optimal weight gain ranges with clinically relevant outcomes not used for the construction of the ranges, we also assessed the associations of the optimal weight gain ranges with low and high birth weight (≤2,500 g or ≥4,000 g). Last, we assessed the clinical performance of both classifications in the external validation sample (n=3505). All statistical tests were 2-sided, with a significance threshold of 0.05. However, the secondary analyses were not adjusted for multiple testing, and therefore these findings should be considered exploratory. Statistical analyses were performed using the Statistical Package of Social Sciences version 24.0 for Windows (SPSS Inc, Chicago, IL, USA) and R statistical software version 3.3.3.

RESULTS

Participant's characteristics

196670 women were included in the main sample (median age (Q1, Q3): 30.0 years (27.0, 33.0)), 40937 (90.1%) European/White) (**Table 1**). 7809 (4.0%), 133788 (68.0%), 38828 (19.7%), 11992 (6.1%), 3284 (1.7%) and 969 (0.5%) had underweight, normal weight, overweight, obesity grade 1, obesity grade 2 and obesity grade 3, respectively. Overall, any adverse outcome occurred in 37.2% (n=73161) of women, ranging from 34.7% (n=2706) in women with underweight to 61.1% (n=592) in women with obesity grade 3. Women who gained more gestational weight had a lower maternal pre-pregnancy BMI, were slightly younger and nulliparous, as compared to multiparous women (**eTable 2**). 169437 women (86.2%) had no missing data for any individual adverse outcome. Of the remainder, 17093 (8.7%) were missing information on gestational hypertensive disorders (including pre-eclampsia and gestational hypertension), 6898 (3.5%) on gestational diabetes, 9786 (5.0%) on caesarean section, 8541 (4.3%) on preterm birth and 6453 (3.3%) on size-for-gestational age at birth (**eTable 3**).

Within the validation sample, 3505 women were included (median age (Q1, Q3): 31.0 years (27.7, 34.7)), 1696 (99.2%) European/White) of whom 277 (7.9%), 2400 (68.5%), 577 (16.5%), 188 (5.4%), 53 (1.5%), and 10 (0.3%) had underweight, normal weight, overweight, obesity grade 1, obesity grade 2 and obesity grade 3, respectively. Any adverse outcome occurred in 1423 (40.6%) of all women (**eTable 4**). 3059 (87.3%) had no missing data for any individual adverse maternal and infant outcomes. Of the remainder, 423 (12.1%) were missing data on gestational hypertensive disorders, 421 (12.0%) on gestational diabetes, 15 (0.4%) on caesarean section, 426 (11.9%) on preterm birth and 7 (0.2%) on size-for-gestational age at birth (**eTable 3**). **eTables 5 and 6** give cohort-specific information. Based on the cohort profiles of all included cohorts, the percentage of women included with multiple singleton pregnancies is about 1%.

Maternal pre-pregnancy BMI, gestational weight gain and absolute risks of adverse outcomes

The absolute risks of any adverse outcome increased across the full range of maternal pre-pregnancy BMI and were largely independent of gestational weight gain (**Figure 1**). The lowest absolute risks were observed among women with low to normal BMI and a moderate to high total gestational weight gain. The lowest risk was 26.7% (n_{cases}/n_{total}=16/60) for women with a BMI <18.0 kg/m^2 and gestational weight gain of 26.0-27.9 kg. The highest absolute risks were observed among women with a high BMI and a high gestational weight gain. The highest risk was 94.4% (n_{cases}/n_{total}=17/18) for women with a BMI ≥40.0 kg/m^2 and gestational weight gain of 20.0-21.9 kg. Among underweight women, the absolute risk of any adverse outcome ranged from 29.2% ($n_{cases/total}$=387/1326) for weight gain of 14.0-15.9 kg to 50.2% ($n_{cases/total}$ =203/404) for weight gain of <8.0 kg (**Figure 2**). Of all outcomes separately, the absolute risk was highest for small size-for-gestational-age (highest risk: 32.1% ($n_{cases/total}$=125/390) for weight gain of <8 kg). Among normal weight women, the absolute risk of any adverse outcome ranged from 31.7% ($n_{cases/total}$ =7314/23073) for weight gain of 14.0-15.9 kg to 46.9%($n_{cases/total}$ =1256/2679) for weight gain ≥28.0 kg and was highest at both extremes of gestational weight gain. Among women with overweight, the absolute risk of any adverse outcome increased from 37.3% ($n_{cases/total}$ =249/667) for weight gain of 2.0-3.9 kg to 56.4% ($n_{cases/total}$ =624/1107) for weight gain of ≥28.0 kg, with the highest risk for caesarean section (highest risk: 25.1% ($n_{cases/total}$=272/1084) for weight gain of ≥28.0 kg). Among women with obesity grades 1 to 3, the absolute risk of any adverse outcome increased over the range of gestational weight gain. The highest absolute risks were 63.7% ($n_{cases/total}$ =160/251) for weight gain of ≥28.0 kg in women with obesity grade 1, 67.7% ($n_{cases/total}$ =384/567) weight gain of ≥16.0 kg in women with obesity grade 2 and 78.8% ($n_{cases/total}$ =93/118) for weight gain of ≥16.0 kg in women with obesity grade 3. The association of maternal pre-pregnancy BMI with the risk of any adverse outcomes was stronger than the association of gestational weight gain (p-value for comparison <0.001). Absolute data for each gestational weight gain category are shown in **eTable 7**.

Optimal gestational weight gain per clinical BMI group

Optimal gestational weight gain ranges are shown in **Figure 3**. Odds Ratios (ORs) and Absolute Risk

Reductions (ARRs) for each weight gain category were 14.0-<16.0 kg for underweight women (Odds Ratio (OR) 0.74 (95% CI: 0.65, 0.84), Absolute Risk Reduction (ARR): 0.07 (95% CI:0.04, 0.09)), 10.0-<18.0 kg for normal weight women (ORs at the outer ends of this range: 0.96 (95% CI: 0.93, 0.99), 0.91 (95% CI: 0.88, 0.95), ARRs: 0.01 (95% CI: 0.00, 0.01), 0.02 (95 % CI: 0.01, 0.03)), 2.0-<16.0 kg for overweight women (ORs at the outer ends of this range: 0.81 (95% CI: 0.69, 0.95) 0.90 (95% CI: 0.85, 0.96), ARRs: 0.05 (95% CI: 0.01, 0.08), 0.02 (95% CI: 0.01, 0.04)), 2.0-<6.0 kg for obesity grade 1 (ORs at the outer ends of this range: 0.76 (95% CI: 0.64, 0.91), 0.73 (95% CI: 0.64, 0.84), ARRs: 0.07 (95% CI: 0.02, 0.11), 0.08 (95% CI: 0.04, 0.11)), weight loss-weight gain of <4.0 kg for obesity grade 2 (median weight loss in this category: -3.0 kg) (ORs at the outer ends of this range: 0.55 (95% CI: 0.39, 0.78), 0.67 (95% CI: 0.51, 0.88),ARRs: 0.14 (95% CI: 0.06, 0.22), 0.10 (95% CI: 0.03, 0.17)) and 0.0-<6.0 kg for obesity grade 3 (ORs at the outer ends of this range: 0.59 (95% CI: 0.41, 0.85), 0.62 (95% CI: 0.41, 0.94), ARRs: 0.12 (95% CI: 0.03, 0.21), 0.10 (95% CI: 0.00, 0.20)) (ORs and ARRs for each weight gain category used to determine the optimal ranges are given in **eTable 8** and **eTable 9**, respectively). **eTable 10** describes the ranges defined in this study and the IOM ranges. Ranges in this study were roughly comparable to IOM ranges for underweight, normal weight and overweight, and lower for all obesity grades. This study classified 11.3% (n=22236) and 33.8% (n=66463) of women in the main sample with inadequate and excessive weight gain, respectively. The IOM categories classified 21.5% (n=42323) and 42.0% (n=82544) with inadequate and excessive gestational weight gain. Gestational weight gain outside the ranges from the current study and IOM was associated with adverse outcomes (**eFigure 2, eFigure 3**). Each classification system had a low to moderate ability to distinguish between those with and without adverse outcomes (Areas-under-the-curve (AUCs): 0.546-0.772) (**eFigure 4**).

Sensitivity analyses

Sensitivity analyses, in which optimal gestational weight gain was determined based on protective associations, regardless of statistical significance, resulted in broader ranges of optimal weight gain (**eFigure 5**). Similar optimal weight gain ranges were observed when length of gestation was considered and when participants with missing individual outcome data were excluded. Sensitivity analyses showed that optimal weight gain definitions were not influenced by including or excluding preterm birth, caesarean section, childhood underweight and overweight, gestational diabetes and pre-eclampsia as adverse outcomes or by adjusting for maternal age and parity (**eTable 11**). **eFigure 6, eTable 12** and **eTable 13** in Supplement show that, 84.6% of participants classified with excessive weight gain in the full pregnancy, would also be classified with excessive weight gain in the first half of pregnancy. Results for the validation sample showed that the discriminative performance of the optimal weight gain definitions developed in this study and weight gain classified according to the IOM guidelines were consistent with findings in the main study sample (AUCs: 0.501-0.788) (**eTable 14, eFigure 7 , eFigure 8**).

DISCUSSION

Maternal pre-pregnancy BMI, and to a lesser extent gestational weight gain, are associated with rates of adverse maternal and infant adverse outcomes. Weight gain ranges that were associated with lower rates of adverse outcomes were 14.0-<16.0 kg for underweight, 10.0-<18.0 kg for normal weight, 2.0-<16.0 kg for overweight, 2.0-<6.0 kg for obesity grade 1, weight loss- weight gain of <4.0 kg for obesity grade 2, and 0.0-<6.0 kg for obesity grade 3. Gestational weight gain outside these ranges was associated with adverse outcomes. However, discriminative performance of gestational weight gain with adverse maternal and infant outcomes was low to moderate. Pre-pregnancy BMI was more strongly associated with adverse maternal and infant outcomes.

Pre-pregnancy BMI is significantly associated with pregnancy complications and offspring obesity and is also associated with gestational weight gain[5,6]. Results from this study suggest that maternal pre-pregnancy BMI was more strongly associated with adverse maternal and infant outcomes and may be an important focus for preconception counseling. Associations of categories of gestational weight gain with adverse outcomes were relatively small. Importantly, associations of women with a pre-pregnancy BMI higher than 36 kg/m^2 and gestational weight gain of more than 20 kg with any adverse outcome approached 95%.

Previous studies attempting to define optimal gestational weight gain associated with fewer adverse outcomes differed considerably in study populations, statistical approaches, outcomes, and conclusions regarding optimal gestational weight gain ranges.[14,16-22] Despite these methodological challenges, five of these studies were included for construction of current IOM guidelines. IOM guidelines are limited by their non-systematic approach, lack of inclusion of maternal pregnancy complications, and lack of consideration of pre-pregnancy obesity severity.[7,21] Only one previous study of 120,251 obese US women defined optimal weight gain ranges according to maternal obesity grade 1 (4.5-11.3 kg), obesity grade 2 (0-4.1 kg) and obesity grade 3 (<4 kg weight loss), and this study used data from term births only.[21] The present study focused on common and important adverse maternal and infant outcomes, included women from multiple Western countries, and compared the associations of gestational weight gain with associations of pre-pregnancy BMI with adverse outcomes. Consistent with IOM guidelines, this study used total gestational weight gain to identify optimal gestational weight gain ranges instead of gestational weight gain per week, since gestational weight gain does not have a linear pattern .[7,8] Total gestational weight gain is dependent on pregnancy duration. The observed results were similar after adjustment for gestational age at birth and after excluding preterm births. Consistent with IOM guidelines, this study showed that among women with higher pre-pregnancy BMI, lower gestational weight gain was associated with fewer adverse outcomes. Gestational weight gain ranges for women with obesity grades 1 to 3 were lower than IOM guidelines and even involved weight loss for severely obese women, although neither classifications were predictive for adverse outcomes. However, results for severely obese women should be interpreted with caution, as optimal gestational weight gain ranges for obesity grades 1-3 associated with better outcomes fluctuate and do not follow a clear linear trend. These results may represent the relatively small sample size of women with obesity and lack of statistical power, rather than biological plausibility. Future studies should evaluate the effect and safety of weight loss during pregnancy in severely obese women.

Gestational weight gain guidelines are used in several Western countries for preconception counseling. Gestational weight gain outside the ranges established in this study and outside the IOM ranges was associated with adverse outcomes. The ranges developed in this study classified fewer women as having suboptimal weight gain compared to the IOM classification. However, the discriminative performance, as indicated by AUC, was very weak for both classifications. This suggests that the use of gestational weight gain guidelines may need to be reconsidered for individual prediction of the risk of adverse outcomes. Further research needs to assess whether optimal weight gain ranges combined with other maternal and fetal pregnancy characteristics are useful for prediction of adverse outcomes.

Findings from this study suggest that pre-pregnancy weight might be a more important target for interventions than gestational weight gain. Previous intervention studies of dietary and physical activity for pregnant women have not shown an effect on pregnancy outcomes.[23-26] Based on current evidence, future clinical trials designed to reduce weight-related maternal and infant adverse outcomes should focus on maternal weight before or at the start of pregnancy.

Limitations

This study has several limitations. First, not all cohorts invited were able to participate in current analyses. Second, analyses did not measure changes in associations of gestational weight gain with adverse outcomes over time. Results may be biased, if the associations of gestational weight gain with adverse outcomes changed over time. Third, data on pre-pregnancy weight was mainly self-reported, and latest weight during pregnancy was either self-reported or measured. This may have led to misclassification of gestational weight gain. Fourth, the composite outcome ‘any adverse outcome’ might have been misclassified as a result of some missing data for adverse individual outcomes. Fifth, all outcomes were considered equally important and analyses did not account for differences in outcome severity. Sixth, caesarean section may be due to many factors and may not be an appropriate outcome for studying associations of weight change with adverse maternal outcomes. [7] Seventh, information on still birth was not available. Eight, optimal weight gain was defined as a protective association with the risk of any adverse outcome, reflecting the best outcome possible and limiting the number of participants incorrectly classified as having adequate weight gain. The ranges would be slightly broader if optimal weight gain was defined as no increased risk of adverse outcomes, which includes both a protective association and null-association. Ninth, analyses were not adjusted for multiple testing. Tenth, as a result of limited sample sizes for underweight and severely obese women, heterogeneity was not assessed. Eleventh, based on the cohort profiles of all included cohorts, about 1% of women were included more than once for multiple pregnancies. Twelfth, for some outcomes, discriminative performance in the validation sample was lower than in the main sample, potentially resulting from overfitting of the models in the main sample.

CONCLUSIONS

In this meta-analysis of pooled individual participant data from 25 cohort studies, the risk of adverse maternal and infant outcomes varied by gestational weight gain and across the range of pre-pregnancy weights. The estimates of optimal gestational weight gain may inform prenatal counseling, although the optimal weight gain ranges had limited predictive value for the adverse outcomes assessed.

AUTHOR CONTRIBUTIONS

Ellis Voerman and Romy Gaillard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Vincent W.V. Jaddoe and Romy Gaillard contributed equally to this work.

Concept and design: Ellis Voerman, Susana Santos, Vincent W.V. Jaddoe, Romy Gaillard

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NINFEA

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PIAMA

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PRIDE Study

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Investigators from the U.S. National Institute of Environmental Health Scientist (NIEHS) were involved in the design of the birth outcomes phase of the FCOU study, but had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. None of the other listed funders had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1. Characteristics of the study population. [a,b]

	Total group	Underweight	Normal weight	Overweight	Obesity grade 1	Obesity grade 2	Obesity grade 3
		(<18.5 kg/m²)	**(18.5-24.9 kg/m²)**	**(25.0-29.9 kg/m²)**	**(30.0-34.9 kg/m²)**	**(35.0-39.9 kg/m²)**	**(≥40.0 kg/m²)**
	n= 196670	**n =7809**	**n= 133788**	**n=38828**	**n=11992**	**n=3284**	**n=969**
Pre-pregnancy body mass index, median (Q1, Q3)[b]	22.7 (20.8, 25.5)	17.9 (17.4, 18.3)	21.8 (20.5, 23.2)	26.8 (25.8, 28.0)	31.8 (30.8, 33.1)	36.7 (35.8, 38)	41.8 (40.8, 43.4)
Total gestational weight gain (kg)							
Median (Q1, Q3)	14.0 (11.0, 18.0)	14.0 (11.0, 17.0)	14.4 (11.6, 18.0)	14.0 (10.0, 18.0)	11.0 (7.0, 16.0)	9.0 (4.5, 13.7)	7.0 (2.0, 12.0)
P2.5, P97.5	4.0, 27.0	6.0, 26.0	6.0, 27.0	2.3, 28.0	0.0, 27.0	-2.4, 25.0	-6.0, 25.0
Maternal age (years), median (Q1, Q3)	30.0 (27.0, 33.0)	29.0 (25.1, 32.0)	30.0 (27.0, 33.0)	30.0 (27.0, 33.3)	30.0 (27.0, 33.0)	30.0 (27.0, 33.3)	30 (27.0, 33.1)
Education[c]							
Low, n (%)	42192 (21.9)	1756 (23.0)	25241 (19.2)	9802 (25.7)	3848 (32.8)	1166 (36.5)	379 (40.7)
Medium, n (%)	78924 (40.9)	3109 (40.7)	52394 (39.9)	16533 (43.4)	5101 (43.5)	1378 (43.2)	409 (43.9)
High, n (%)	71819 (37.2)	2780 (36.4)	53724 (40.9)	11736 (30.8)	2786 (23.7)	649 (20.3)	144 (15.5)
Country							
Norway, n (%)	74507 (37.9)	2154 (27.6)	49388 (36.9)	16224 (41.8)	5013 (41.8)	1360 (41.4)	368 (38.0)
Denmark, n (%)	60963 (31.0)	2583 (33.1)	41344 (30.9)	11930 (30.7)	3762 (31.4)	1024 (31.2)	320 (33.0)
The Netherlands, n (%)	14861 (7.6)	531 (6.8)	10329 (7.7)	2841 (7.3)	860 (7.2)	235 (7.2)	65 (6.7)
United Kingdom, n (%)	12610 (6.4)	521 (6.7)	8948 (6.7)	2232 (5.7)	659 (5.5)	191 (5.8)	59 (6.1)
Portugal, n (%)	7220 (3.7)	293 (3.8)	4783 (3.6)	1525 (3.9)	454 (3.8)	129 (3.9)	36 (3.7)
Italy, n (%)	5307 (2.7)	428 (5.5)	3893 (2.9)	725 (1.9)	209 (1.7)	50 (1.5)	2 (0.2)
Germany, n (%)	5099 (2.6)	269 (3.4)	3889 (2.9)	699 (1.8)	183 (1.5)	46 (1.4)	13 (1.3)
Ukraine, n (%)	3261 (1.7)	303 (3.9)	2360 (1.8)	479 (1.2)	102 (0.9)	16 (0.5)	1 (0.1)
Greece, n (%)	2872 (1.5)	163 (2.1)	2088 (1.6)	463 (1.2)	118 (1.0)	33 (1.0)	7 (0.7)
Spain, n (%)	1933 (1.0)	89 (1.1)	1351 (1.0)	344 (0.9)	99 (0.8)	36 (1.1)	14 (1.4)
United States, n (%)	2021 (1.0)	78 (1.0)	1192 (0.9)	440 (1.1)	195 (1.6)	74 (2.3)	42 (4.3)
Poland, n (%)	1702 (0.9)	163 (2.1)	1299 (1.0)	191 (0.5)	41 (0.3)	7 (0.2)	1 (0.1)
Finland, n (%)	1406 (0.7)	39 (0.5)	945 (0.7)	254 (0.7)	119 (1.0)	31 (0.9)	18 (1.9)
Slovakia, n (%)	983 (0.5)	119 (1.5)	681 (0.5)	130 (0.3)	44 (0.4)	9 (0.3)	0 (0.0)
Canada, n (%)	844 (0.4)	37 (0.5)	494 (0.4)	166 (0.4)	86 (0.7)	38 (1.2)	23 (2.4)

[a] Values are median (Q1, Q3), median (P2.5, P97.5) or n (valid %).

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared and is categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obesity grade 1 (30.0-34.9 kg/m^2), obesity grade 2 (35.0-39.9 kg/m^2), and obesity grade 3 (≥40.0 kg/m^2).

[c] Education level was based on cohort-specific criteria. Each cohort used their own country-specific criteria to define low, medium and high educational level. These 3 categories were subsequently used in the meta-analysis.

Table 1. Characteristics of the study population (continued). [a,b]

	Total group	Underweight	Normal weight	Overweight	Obesity grade 1	Obesity grade 2	Obesity grade 3
		(<18.5 kg/m^2)	(18.5-24.9 kg/m^2)	(25.0-29.9 kg/m^2)	(30.0-34.9 kg/m^2)	(35.0-39.9 kg/m^2)	(≥40.0 kg/m^2)
	n= 196670	n =7809	n= 133788	n=38828	n=11992	n=3284	n=969
Gestational hypertension, n (%)[c]	6683 (3.9)	151 (2.2)	3583 (3.0)	1776 (5.2)	807 (7.8)	284 (10.3)	82 (10.5)
Pre-eclampsia, n (%)[d]	5996 (3.5)	112 (1.7)	3067 (2.6)	1637 (4.8)	781 (7.6)	287 (10.4)	112 (13.9)
Gestational diabetes, n (%)[e]	2946 (1.6)	57 (0.8)	1407 (1.1)	818 (2.2)	420 (3.6)	183 (5.8)	61 (6.6)
Caesarean section, n (%)	29567 (15.8)	927 (12.6)	17825 (14.1)	6944 (18.7)	2685 (23.3)	882 (27.8)	304 (32.7)
Preterm birth, n (%)[f]	8250 (4.4)	383 (5.3)	5314 (4.2)	1664 (4.4)	643 (5.5)	177 (5.5)	69 (7.2)
Small size-for-gestational-age, n (%)[g]	19030 (10.0)	1336 (17.9)	13527 (10.5)	2963 (7.8)	900 (7.7)	224 (7.0)	80 (8.5)
Large size-for-gestational-age, n (%)[h]	2542 (10.0)	256 (3.4)	10789 (8.4)	5099 (13.5)	1995 (17.0)	649 (20.3)	217 (23.0)
Childhood underweight, n (%)[i]	2542 (2.0)	196 (4.2)	1865 (2.2)	367 (1.5)	88 (1.2)	20 (1.0)	6 (1.1)
Childhood overweight, n (%)[j]	21718 (17.2)	348 (7.5)	12263 (14.2)	5814 (23.4)	2328 (31.6)	722 (37.0)	243 (43.2)
Any adverse outcome, n (%)[k]	73161 (37.2)	2706 (34.7)	45687 (34.1)	16292 (42.0)	6019 (50.2)	1865 (56.8)	592 (61.1)

[a] Values are median (Q1, Q3), median (P2.5, P97.5) or n (valid %).

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared and is categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obesity grade 1 (30.0-34.9 kg/m^2), obesity grade 2 (35.0-39.9 kg/m^2), and obesity grade 3 (≥40.0 kg/m^2).

[c] Gestational hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation in previously normotensive women.

[d] Pre-eclampsia is defined as gestational hypertension plus proteinuria.

[e] Gestational diabetes is defined as either a random glucose level >11.0 mmol/L, a fasting glucose level ≥7.0 mmol/L or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test (glucose level >7.8 mmol/L after glucose intake).

[f] Preterm birth is defined as gestational age at birth <37 weeks.

[g] Small size-for-gestational-age at birth is defined as sex- and gestational age adjusted birth weight <10th percentile.

[h] Large size-for-gestational-age at birth is defined as sex- and gestational age adjusted birth >90th percentile.

[i] Childhood underweight at the highest age available for each child (median (Q1, Q3): 84.9 (61.9, 95.9) months) is defined as sex- and age adjusted standard deviation scores (SDS) <-2.0 SDS for children of 2-5 years of age, and <-2.0 SDS for children of >5 years.

[j] Childhood overweight at the highest age available for each child (median (Q1, Q3): 84.9 (61.9, 95.9) months) is defined as sex- and age adjusted standard deviation scores (SDS) >2.0 SDS for children of 2-5 years of age, and >1.0 SDS for children of >5 years.

[k] Any adverse outcome includes pre-eclampsia, gestational hypertension, gestational diabetes, caesarean section, preterm birth, small size-for-gestational-age, and large size-for-gestational-age

FIGURE LEGENDS

Figure 1. Heatmap showing absolute risks of any adverse maternal and infant outcome across the full ranges of maternal body mass index and gestational weight gain.

Values represent the absolute risks of any adverse maternal and infant outcome (left figure) and the percentages of participants (right figure) for each combination of body mass index and gestational weight gain. Absolute risks were calculated as (n (any outcome) / n (body mass index and gestational weight gain category))*100. The percentages of participants are the number of participants in each cell as a percentage of the total study sample (n=196670). Participants in the extreme categories of pre-pregnancy BMI and gestational weight gain had values beyond the most extreme labeled tick marks. Body mass index is calculated as weight in kilograms divided by height in meters squared. Any adverse outcome includes pre-eclampsia, gestational hypertension, gestational diabetes, caesarean section, preterm birth, small size-for-gestational-age, and large size-for-gestational-age. Gestational hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation in previously normotensive women. Pre-eclampsia is defined as gestational hypertension plus proteinuria. Gestational diabetes is defined as either a random glucose level >11.0 mmol/L, a fasting glucose level ≥7.0 mmol/L or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test (glucose level >7.8 mmol/L after glucose intake). Preterm birth is defined as gestational age at birth <37 weeks. Small and large size-for-gestational-age at birth are defined as sex- and gestational age adjusted birth weight <10th percentile and >90th percentile, respectively.

Figure 2. Absolute risks of adverse maternal and infant outcomes across the full range of gestational weight gain by clinical maternal body mass index group.

The symbols represent the absolute risks of adverse maternal and infant outcomes (absolute risks) within each gestational weight gain category for women with (A) underweight, (B) normal weight, (C) overweight, (D) obesity grade 1, (E) obesity grade 2 and (F) obesity grade 3. The symbols represent the mean for all participants in each gestational weight gain category. The percentages below each of the figures represent the number of participants in that gestational weight gain category as a percentage of all participants within that BMI category. Participants in the extreme categories of gestational weight gain had values beyond the most extreme labeled tick marks. Absolute risks were calculated as (n (outcome) / n (gestational weight gain category within BMI group))*100. Body mass index is calculated as weight in kilograms divided by height in meters squared. Maternal body mass index is categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obesity grade 1 (30.0-34.9 kg/m^2), obesity grade 2 (35.0-39.9 kg/m^2), and obesity grade 3 (≥40.0 kg/m^2). Gestational hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation in previously normotensive women. Pre-eclampsia is defined as gestational hypertension plus proteinuria. Gestational diabetes is defined as either a random glucose level >11.0 mmol/L, a fasting glucose level ≥7.0 mmol/L or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test (glucose level >7.8 mmol/L after glucose intake). Preterm birth is defined as gestational age at birth <37 weeks. Small and large size-for-gestational-age at birth are defined as sex- and gestational age adjusted birth weight <10th percentile and >90th percentile, respectively. Any adverse outcome includes pre-eclampsia, gestational hypertension, gestational diabetes , caesarean section, preterm birth, small size-for-gestational-age, and large size-for-gestational-age. Odds ratios for the risk of any adverse outcome per SD increase in maternal pre-pregnancy BMI and gestational weight gain were 1.28 (95% CI: 1.27, 1.29) and 1.04 (95% CI: 1.03, 1.05), respectively. P-value for comparison: <0.001.

eTable 7 in Supplement shows the number of cases of each outcome and the total number of participants in each gestational weight gain category.

Figure 3. Associations of gestational weight gain categories with any adverse outcome per maternal clinical body mass index group, used to determine optimal weight gain ranges.

The symbols represent odds ratios (OR) 95% Confidence Intervals (CI)) reflecting the risk of any adverse outcome per gestational weight gain category for women with (A) underweight, (B) normal weight, (C) overweight, (D) obesity grade 1, (E) obesity grade 2 and (F) obesity grade 3, as compared to all other gestational weight gain categories in that specific clinical maternal body mass index group. The symbols represent the mean for all participants in each gestational weight gain category. The percentages below each of the figures represent the number of participants in that gestational weight gain category as a percentage of all participants within that BMI category. Participants in the extreme categories of gestational weight gain had values beyond the most extreme labeled tick marks. The ORs are presented on a log scale. Body mass index is calculated as weight in kilograms divided by height in meters squared. Maternal body mass index is categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obesity grade 1 (30.0-34.9 kg/m^2), obesity grade 2 (35.0-39.9 kg/m^2), and obesity grade 3 (≥40.0 kg/m^2). Any adverse outcome includes pre-eclampsia, gestational hypertension, gestational diabetes, caesarean section, preterm birth, small size-for-gestational-age, and large size-for-gestational-age. Gestational hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation in previously normotensive women. Pre-eclampsia is defined as gestational hypertension plus proteinuria. Gestational diabetes is defined as either a random glucose level >11.0 mmol/L, a fasting glucose level ≥7.0 mmol/L or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test (glucose level >7.8 mmol/L after glucose intake). Preterm birth is defined as gestational age at birth <37 weeks. Small and large size-for-gestational-age at birth are defined as sex- and gestational age adjusted birth weight <10th percentile and >90th percentile, respectively. For the ranges defined in this study , a statistically significant OR lower than 1 for a gestational weight gain category was considered optimal weight gain. If a non-significant association (either with an OR above or below or exactly one) for a weight gain category was surrounded by two significant estimates with an OR below 1, that weight gain category was included in the optimal weight gain range. The red area represents the optimal weight gain range according to the current analysis, the grey area represents the weight gain ranges as recommended by US Institute of Medicine (IOM). **eTable 7** in Supplement shows the number of cases of each any adverse outcome and the total number of participants in each gestational weight gain category**. eFigure 5** in Supplement shows the optimal gestational weight gain ranges based on a protective associations only.

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